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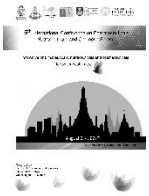

In *vitro* Characterization of Matrix-Controlled Release Ambroxol Capsules Containing Lipophilic Excipients

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Introduction

Ambroxol hydrochloride (ABX) is an active metabolite of mucolytic agent bromhexine and is used in the treatment of bronchitis to improve expectoration. It is rapidly absorbed after oral administration followed by an elimination with a half-life of 3–4 h, requiring three dosings per day for optimum therapeutic efficacy.[1] There are a numerous research studies which have been developed a dosage forms to improve patient compliance, based on controlled release tablet, pellet or capsule dosage forms allowing once daily administration.[2] A hydrophilic, hydrophobic and hydrophilic/hydrophilic matrix dosage forms such as tablets and capsules have been widely used in the formulation of controlled- release oral solid dosage forms. The hydrophilic polymers i. e. , hydroxypropylmelthylcellulose (HPMC) and methylcellulose (MC) are exposed to an aqueous medium without disintegration, the immediate hydration is formed a highly viscous surface barrier to control the drug release by diffusion mechanism.[3] The liquid penetration has to be conduct into the matrix systems before drug release. The hydrophobic materials, i.e. waxes, lipids have been also used for matrix formulation. The lipophilic materials chosen as matrix carriers are erodible polar lipids to decrease liquid penetration of dosage form, resulting in the control of drug release. The erosion is the main mechanism for controlled release systems of lipid excipients. The melting point of lipid excipients is in the range of 55-99°C, suggests they can melt and prepared by the fusion process. The combination of hydrophilic polymers and hydrophilic polymers may alter the drug release mechanism and rate. The lipophilic materials such as carnauba wax (CW), white beeswax (WB) or stearyl alcohol (SA) may modify the drug release by change type and amount of lipid compounds. Lipids may be suitable in this way as release modifiers for incorporation into cellulose matrices such as HPMC.

The purpose of this study was to examine the in *vitro* characterization of matrix-controlled release ABX capsules containing lipophilic excipients (CW, WB and SA) at the various amounts and HPMC. The capsules were prepared by melting of lipophilic excipients and physical mixing the powders before filling into the capsules. In *vitro* characterization of capsules, including weight variation, ABX content, dissolution profiles and release kinetics was evaluated. The optimal capsule formulations were further investigated the difference factor (f_1) and similarity factor (f_2) of dissolution profiles compared to marketed product (Mucosolvan® PL).

Methods

Preparation of ABX capsules

The ABX (Vitalife Laboratories, India) and HPMC (Methocel® F4M, Srichand-united dispensary Ltd, Thailand) powders were accurate weighted and geometrically mixed, as shown in Table 1. The various amount of lipophilic excipients i.e., CW, WB and SA were melted above the melting point using oil bath with temperature controller. Then, molten mass was immediately poured in to the powder mixture and added up with corn starch (Saguanchai Chemical Import co. Ltd, Thailand). Final powders were filled into hard gelatin capsules of size 1 in a lab scale capsule filling machine (Semiautomatic Capsule Filling Machine 2 (Model Panviv A-01). All capsules were stored in a desiccator before the evaluation.

Evaluations of ABX capsules

Weight variation: Each capsule was accurate weighed by analytical balance. The average weight and standard deviation were calculated.

The ABX assay: Twenty capsules were taken randomly, opened and poured in a mortar. A portion of the crushed powder was weighed and transferred into a 100 volumetric flask containing a portion of methanol (AR grade, RCI Lab Scan, Ltd, Thailand). The mixture was stirred on a magnetic stirrer, diluted and adjusted the volume with methanol and then assayed using UV-visible spectrophotometer (Spectronic® Genesyn 5, Rochester, U.S.A.) at a wavelength of 307.5 nm. The ABX content was calculated and expressed a % labeled amount.

In *vitro* dissolution test: The release of ABX from capsules was determined using United States Pharmacopeia (USP) dissolution testing apparatus I (basket method; Disket Dissolution Model 2100) The dissolution test was performed using 1000 ml of pH 1.2 for the first 2 h and phosphate buffer pH 6.8 from 2-12 h at 37 ± 0.5°C at 100 rpm of stirring. Ten milliliter of sample was withdrawn and replaced with fresh dissolution medium. The solution samples were measured at 307.5 nm using UV-visible spectrophotometer. The dissolution experiments were carried out in triplicate. The marketed product (Mucosolvan® PL) was also evaluated to compare the release profile with ABX capsules.

Drug release kinetics: In order to understand the kinetics of drug release, the drug release data of in *vitro* dissolution study was analyzed with various kinetic equations i.e., zero-order (% drug release versus time), first- order (Log % drug retained versus time) and Higuchi's equation. The coefficient of determination (r^2) values was calculated for the linear curves obtained by regression analysis of the above plots**.**

Model independent approach using a similarity factor: A model-independent mathematical method was developed by Moore and Flanner for comparison of dissolution profiles using a difference factor (f_1) and a similarity factor (f_2) to compare dissolution profiles.[4]

The difference factor (f_1) calculates the percent (%) difference between the two curves at each time point and is a measurement of the relative error between the two curves:

$$\square_{\square} = \left\{ \frac{[\sum_{\square=1}^{\square} |\square_{\square} - \square_{\square}|]}{\sum_{\square=1}^{\square} \square_{\square}} \right\} \cdot 100$$

The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves. The factor f_2 measures the closeness between the two profiles:

$$\square_2 = 50 \cdot \log \left\{ \left[1 + \frac{1}{\square} \sum_{\square=1}^{\square} (\square_{\square} - \square_{\square})^2 \right]^{-0.5} \times 100 \right\}$$

where n is the number of time points, R_t is the dissolution value of the reference (marketed product) batch at time t, and T_t is the dissolution value of the test (ABX capsules) batch at time t**.**

Table 1 The formula of ABX capsules

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
ABX (mg)	75	75	75	75	75	75	75	75	75	75	75
HPMC (mg)	-	50	50	50	50	50	50	50	50	50	50
CW (%)	-	-	10	30	50	-	-	-	-	-	-
WB (%)	-	-	-	-	-	10	30	50	-	-	-
SA (%)	-	-	-	-	-	-	-	-	10	30	50
Corn starch	qs										

Results and Discussion

The ABX capsules were successfully prepared. All capsules weight was in the range of 218-264 mg. The percent labeled amount was in the range of 92.48-109.89 %, that was within the assay limit (90-110%) specified in the monograph of USP [5], as shown in Table 2. These results indicated that capsules had good characteristics of capsules.

Table 2 Percent labeled amount and weight variation of ABX capsules

Formulation	Labeled amount (%)	Weight (mg)
F1	92.48 ± 2.55	235.29 ± 2.46
F2	109.14 ± 3.81	238.35 ± 0.59
F3	109.89 ± 0.67	244.80 ± 4.15
F4	92.93 ± 1.57	247.81 ± 4.83
F5	109.59 ± 4.12	264.82 ± 9.17
F6	97.43 ± 8.46	242.96 ± 7.66
F7	106.89 ± 1.81	243.59 ± 7.54
F8	104.19 ± 0.50	218.06 ± 7.34
F9	102.84 ± 3.15	236.63 ± 4.85
F10	93.34 ± 2.39	234.54 ± 4.32
F11	102.39 ± 1.53	234.80 ± 5.54

The ABX dissolution profiles were shown in Figure 1. Results revealed the effect of type and concentration of lipophilic excipients on ABX released from capsule with function of time. The capsules containing free drug (F1) released 100% within 10 min. This was due to the very soluble property of drug in the dissolution medium, whereas, the incorporation of the hydrophilic polymer (HPMC) into the formulation (F2), the slow release of ABX was obtained (66.37% of ABX within 12 h). The addition of the third component into the system was introduced. The lipophilic excipients i.e., CW, WB or SA was incorporated in order to combined the hydrophilic and lipophilic property into the system. Figure 1 (A1-A3) established the effect of amount of lipophilic excipients on the release of ABX capsule. The slow release of ABX was clearly seen with increasing the amount of lipophilic compartment. Formulation containing 50% of lipophilic substances displayed the lowest release of ABX, while the fastest released is found in formulation containing 10% of lipophilic substances. These results explained that lipophilic excipients delayed the hydration, wetting and swelling of hydrophilic carrier to promote the diffusion of ABX from the capsules.[6] The lipophilic excipients were eroded during the ABX release. Figure 1 (B1-B3) also displays the effect of type of lipophilic excipients on the ABX release. At 10 % of lipophilic substances, the released of ABX was around 78.21, 92.35, and 94.17 % for CW, WB and SA, respectively. The similar trend of ABX released was found for 30 and 50% of lipophilic substances. These results demonstrated that at the same concentration (10, 30 or 50% of lipophilic substances), the release of ABX from capsules was not clearly seen the effect of type of lipophilic excipients on dissolution profile. The type of lipophilic substances may the important factor on the release of drug.

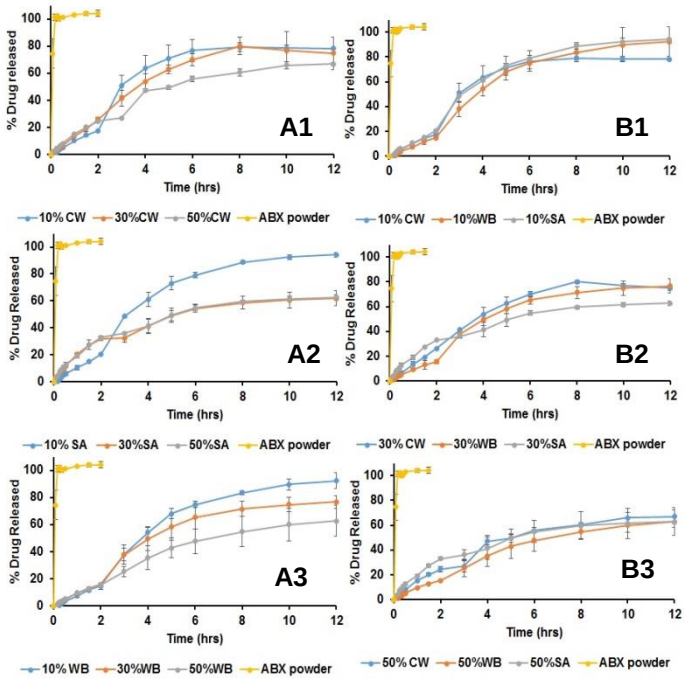

Figure 1 Drug release from ABX capsules containing lipophilic excipients, A1, CW: carnauba wax, A2, SA: stearyl alcohol, A3, WB: white beeswax at concentration 10%, 30% 50%, B1, 10%, B2, 30% and B3, 50% of lipophilic excipients in 0.1 N HCl (for first 2 h) and phosphate buffer pH 6.8 (2-12 h). Data are presented as mean ± SD (n=3).

The different factor (f_1) and similarity factor (f_2) was further determined the effect of type of lipophilic excipients on dissolution profile. For curves to be considered similar, f_1 values should be close to 0, and f_2 values should be close to 100. Generally, f_1 values up to 15 (0-15) and f_2 values greater than 50 (50-100) ensure sameness or equivalence of the two curves. [7] Capsules containing 50% of lipophilic compounds were selected to determine f_1 and f_2 values as shown in Table 3. Capsule with CW provided the most similar to marketed product. These were because CW and HPMC were a best suitable component to form the matrices with ABX and conduce the release of ABX by diffusion. [8] These results were supported by a study of kinetic models. The in vitro drug release data were fitted into different release kinetic models i.e., zero order, first order, Higuchi model. The results showed that the release kinetic of all formulation intend to Higuchi model as seen in Table 4. The coefficient of determination (r^2) serves as a good indicator of the mechanism that best explains drug release from the various matrices. These results indicated the 50 % lipophilic CW was the best controlled release matrix capsule with the good physical properties.

Table 3 The different and similarity factors of ABX capsule compared to marketed product

Formulation	f_1	f_2
F5 (50% CW)	10.30	71.42
F8 (50% WB)	13.92	66.08
F11 (50% SA)	11.33	64.95

Table 4 Release kinetics of ABX capsules

Formulation	r^2		
	Zero order	First order	Higuchi
F3	0.8285	0.5767	0.9158
F4	0.8695	0.6131	0.9531
F5	0.8747	0.6540	0.9735
F6	0.9231	0.6722	0.9472
F7	0.9054	0.7082	0.9526
F8	0.9443	0.7038	0.9753
F9	0.9017	0.6444	0.9492
F10	0.8646	0.6444	0.9760
F11	0.8626	0.6160	0.9779

Conclusion

The matrix-controlled release ABX capsules formulated by lipophilic excipients were successfully prepared. In *vitro* characterization of capsules including ABX content, weight variation and dissolution profiles revealed that capsules were good matrix capsules. Capsules containing a suitable amount and type of lipophilic excipients provided a correlation of dissolution profile with the marketed product. A sustained release was achieved. These results suggest that the lipophilic excipients may potentially be used as excipients for controlled delivery of highly soluble ABX.

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